B. REMARKS

Reconsideration of the above-identified application is respectfully requested.

Claims 6-8 stand rejected under 35 U.S.C. 101 because the claimed invention is not supported either by a well-asserted utility or a well-established utility. This rejection is respectfully traversed.

The present invention, as defined broadly in Claim 6, is directed to a method of engrafting mesenchymal stem cells, comprising administering mesenchymal stem cells to a fetus in utero. The fetus may be a non-human fetus, as defined in Claim 7, and the mesenchymal stem cells may be human mesenchymal stem cells, as defined in Claim 8.

The Examiner has admitted that the specification teaches and provides evidence that mesenchymal stem cells can be transplanted in utero, and that the implanted cells will become distributed throughout the fetus, and in some cases, the cells differentiate into various cell types.

As indicated in the specification, human mesenchymal stem cells were given to fetal sheep at 65 days or 85 days gestation. Tissue was harvested from the sheep at 2 weeks, 2 months, or 5 months after transplantation of the human mesenchymal stem cells.

Two weeks after the transplantation of the human mesenchymal stem cells, human β-2 microglobulin DNA was detected in liver, spleen, lung, bone marrow, thymus, brain, heart, and blood in both the sheep that were given the mesenchymal stem cells at 65 days gestation, and the sheep that were given the mesenchymal stem cells at 85 days gestation.

After. 2 months, human DNA was detected in liver, spleen, lung, bone marrow, thymus, heart, skeletal muscle, blood, and cartilage of fetuses transplanted with the human mesenchymal stem cells at 65 days gestation. In the fetuses transplanted at 85 days gestation, human DNA was detected after 2 months in the spleen, bone marrow, thymus, and blood.

At 5 months after the in utero transplantation of the human mesenchymal stem cells, i.e., at 3 months after birth, human DNA was detected in the bone marrow, thymus, spleen, lung, cartilage, and blood of fetuses transplanted at 65 days gestation, and in the heart, brain, skeletal muscle, and blood of fetuses transplanted at 85 days gestation.

Furthermore, as discussed at Pages 22 and 23 of the specification, the human mesenchymal stem cells, after the administration thereof to fetal sheep, were found to have differentiated into cardiomyocytes, chondrocytes, bone marrow stromal cells, and thymic stromal cells.

In particular, at 2 and 5 months after in utero transplantation, human cells were detected in the cardiac muscle of sheep fetuses transplanted at 65 and 85 days gestation. Such cells had similar morphology to the surrounding ovine cardiomyocytes.

In addition, chondrocyte differentiation was identified by the finding of human β-2 microglobulin positive cells in the cartilage lacunae of lambs transplanted with human mesenchymal stem cells at 65 days gestation, and harvested at 2 months or 5 months after transplantation.

At 5 months after in utero transplantation of human mesenchymal stem cells, many human cells were seen in the bone marrow of the sheep, and were demonstrated to express CD23. The human CD23 positive cells appeared to be

large cells clustered in areas with sheep hematopoietic elements, consistent with bone marrow stroma.

Furthermore, at 5 months after in utero transplantation of human mesenchymal stem cells, multiple human cells were detected in the thymus that expressed CD74, an MHC associated invariate chain expressed on thymic stromal cells. These cells were large and were similar in morphologic appearance to nearby ovine thymic epithelium.

At Page 24, it is noted that in five fetal sheep at 65 days gestation in which tail wounds were created and which were given human mesenchymal stem cells human DNA was found in the tail wounds, and such cells in which the human DNA was found had the morphological appearance of fibroblasts.

Thus, Applicants clearly have demonstrated that one can transplant mesenchymal stem cells into a fetus in utero, and that the mesenchymal stem cells will engraft in the fetus, and may differentiate into various cell types in the fetus. Thus, the results shown in the specification provide a basis for employing prenatal mesenchymal stem cell transplantation in order to provide a reservoir of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage, as stated at Page 25 of the specification.

Therefore, contrary to the Examiner's assertions, the claimed method has a specific and substantial asserted utility.

The Examiner again is reminded that the claims define a method of engrafting mesenchymal stem cells, and through the examples, Applicants have demonstrated that one may engraft mesenchymal stem cells into a fetus, and further that such engrafted mesenchymal stem cells may differentiate in the fetus into various cell types. Furthermore, the Examiner is reminded that Applicants

need not demonstrate every possible utility of the invention, and the burden is upon the Examiner to show that the claimed method has no utility. The case law is clear that not all embodiments encompassed within a claim must be operable for the claim to be valid. (Ex parte Mark, 12 U.S. P.Q. 2d 1904 (Bd. App. Int. 1989).) The Examiner has not met such burden in that, in order to assert that the claimed invention has no utility, the Examiner has provided nothing more than statements of sheer speculation.

Thus, because Applicants have demonstrated engraftment and differentiation of mesenchymal stem cells when such mesenchymal stem cells have been transplanted into a fetus, Applicants have demonstrated a utility for the claimed invention, especially where the Examiner has failed to show that the claimed invention does not have any utility. Therefore, Claims 6-8 comply with the requirements of 35 U.S.C. 101, and it is therefore respectfully requested that the rejection under 35 U.S.C. 101 be reconsidered and withdrawn.

Claims 6-8 stand rejected under 35 U.S.C. 112, first paragraph. This rejection is respectfully traversed.

The Examiner has taken the position that the specification provides insufficient guidance and teaching on how to accomplish the proposed utilities specifically set forth.

In response, as stated hereinabove, Applicants have demonstrated that mesenchymal stem cells, when administered to a fetus, will engraft in the fetus, and such mesenchymal stem cells will differentiate into various cell types. Thus, the mesenchymal stem cells may be used to provide a reservoir of normal stem cells to replace defective cells as they become damaged in degenerative diseases with progressive cellular and organ damage. The examples have shown that mesenchymal stem cells, when transplanted into a fetus, may differentiate into cardiomyocytes, chondrocytes, bone marrow stromal cells, and

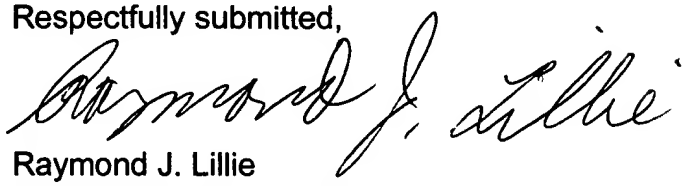
thymic stromal cells. Thus, Applicants have proven the principle that one can transplant mesenchymal stem cells into a fetus, whereby the mesenchymal stem cells will engraft in the fetus, and such mesenchymal stem cells will differentiate into various cell types. Thus, there is a reasonable expectation that one can administer mesenchymal stem cells to a fetus, and that such mesenchymal stem cells will engraft and then differentiate in vivo into various cell types, and thus such mesenchymal stem cells may be used to replace defective cells. The working examples, therefore, provide sufficient guidance with respect to practicing the claimed invention, and also provide one skilled in the art with a reasonable expectation of success.

The Examiner, in holding that the specification does not provide an enabling disclosure, has provided nothing more than statements of sheer speculation. Such speculative statements are insufficient to support the Examiner's holding.

Therefore, for the above reasons and others, the specification provides an enabling disclosure, and it is therefore respectfully requested that the rejection under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

For the above reasons and others, this application is in condition for allowance, and it is therefore respectfully requested that the rejections be reconsidered and withdrawn and a favorable action is hereby solicited.

Respectfully submitted,



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